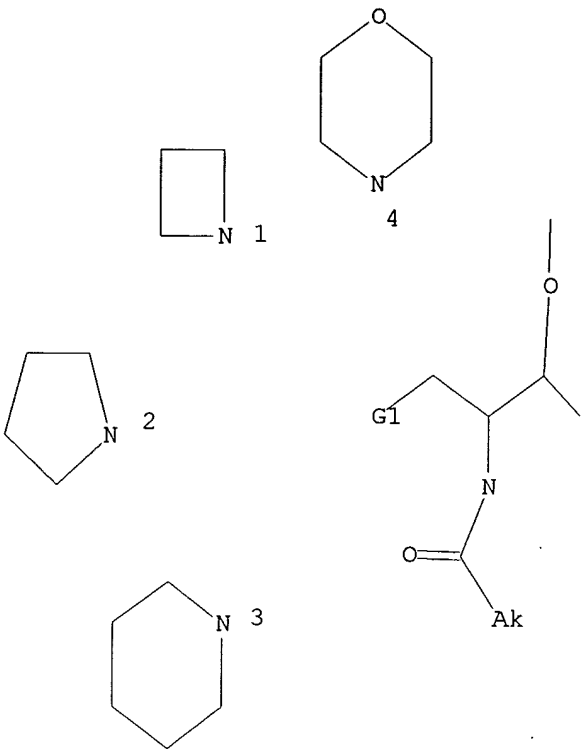
ploading 10044869.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 [@1],[@2],[@3],[@4]

Structure attributes must be viewed using STN Express query preparation.

=>
Uploading 10044869.str

L2 STRUCTURE UPLOADED

=> s l2 full
FULL SEARCH INITIATED 16:05:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 11768 TO ITERATE

100.0% PROCESSED 11768 ITERATIONS 786 ANSWERS
SEARCH TIME: 00.00.02

L3 786 SEA SSS FUL L2

=>
Uploading 10044869.str

L4 STRUCTURE UPLOADED

=> d

```
L4 HAS NO ANSWERS
L4              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l4 full
FULL SEARCH INITIATED 16:09:34 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      2 TO ITERATE

100.0% PROCESSED       2 ITERATIONS                                    0 ANSWERS
SEARCH TIME: 00.00.01

L5            0 SEA SSS FUL L4

=>
Uploading 10044869.str

L6      STRUCTURE UPLOADED

=> s l6 full
FULL SEARCH INITIATED 16:10:14 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     88 TO ITERATE

100.0% PROCESSED      88 ITERATIONS                                    0 ANSWERS
SEARCH TIME: 00.00.01

L7            0 SEA SSS FUL L6

=>
Uploading 10044869.str

L8      STRUCTURE UPLOADED

=> d
L8 HAS NO ANSWERS
L8              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l8 full
FULL SEARCH INITIATED 16:18:36 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    883 TO ITERATE

100.0% PROCESSED     883 ITERATIONS                                    0 ANSWERS
SEARCH TIME: 00.00.01

L9            0 SEA SSS FUL L8

=>
Uploading 10044869.str

L10     STRUCTURE UPLOADED

=> d
L10 HAS NO ANSWERS
L10             STR
```

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

```
=> s l10
SAMPLE SEARCH INITIATED 16:19:37 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     54 TO ITERATE

100.0% PROCESSED      54 ITERATIONS                          1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          640 TO     1520
PROJECTED ANSWERS:               1 TO       80

L11           1 SEA SSS SAM L10

=> s l10 full
FULL SEARCH INITIATED 16:19:41 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    883 TO ITERATE

100.0% PROCESSED     883 ITERATIONS                         34 ANSWERS
SEARCH TIME: 00.00.01

L12          34 SEA SSS FUL L10
```

> S 113008-18-7/RN
L1 1 113008-18-7/RN

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.20	1.41

FILE 'CAPLUS' ENTERED AT 17:45:44 ON 03 FEB 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 3 Feb 2003 VOL 138 ISS 6
FILE LAST UPDATED: 2 Feb 2003 (20030202/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> S L1/THU
1 L1
488671 THU/RL
L2 0 L1/THU
(L1 (L) THU/RL)

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.14	3.55

FILE 'CAPLUS' ENTERED AT 17:46:24 ON 03 FEB 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 3 Feb 2003 VOL 138 ISS 6
FILE LAST UPDATED: 2 Feb 2003 (20030202/ED)

This file contains CAS Registry Numbers for easy and accurate

substance identification.

```
=> S L1
L3            1 L1

=> DIS L3 1 IBIB ABS

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         1988:128158  CAPLUS
DOCUMENT NUMBER:          108:128158
TITLE:                    Scytonemin A, a novel calcium antagonist from a
                          blue-green alga
AUTHOR(S):                Helms, Gregory L.; Moore, Richard E.; Niemczura,
                          Walter P.; Patterson, Gregory M. L.; Tomer, Kenneth
                          B.; Gross, Michael L.
CORPORATE SOURCE:         Dep. Chem., Univ. Hawaii, Honolulu, HI, 96822, USA
SOURCE:                   Journal of Organic Chemistry (1988), 53(6), 1298-307
                          CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
GI
```

Uploading 10044869.str

L1 STRUCTURE UPLOADED

=> s l1 full
FULL SEARCH INITIATED 11:54:02 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 883 TO ITERATE

100.0% PROCESSED 883 ITERATIONS 34 ANSWERS
SEARCH TIME: 00.00.01

L2 34 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 148.15 148.36

FILE 'CAPLUS' ENTERED AT 11:54:07 ON 04 FEB 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 4 Feb 2003 VOL 138 ISS 6
FILE LAST UPDATED: 3 Feb 2003 (20030203/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2 and glucos?
6 L2
410594 GLUCOS?
L3 0 L2 AND GLUCOS?

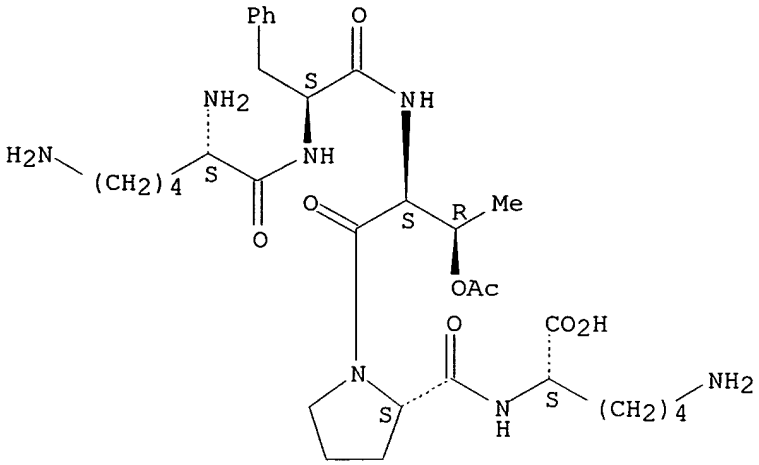
=> s l2 and glycos?
6 L2
137795 GLYCOS?
L4 0 L2 AND GLYCOS?

=> s l2 and ?ceramid?
6 L2
11253 ?CERAMID?
L5 0 L2 AND ?CERAMID?

=> s l2 and sphingo?
6 L2
20441 SPHINGO?
L6 0 L2 AND SPHINGO?

=> s l2 and cancer

```
            6 L2
       179056 CANCER
        24995 CANCERS
       186179 CANCER
                (CANCER OR CANCERS)
L7          0 L2 AND CANCER

=> s l2 and ?gluco?
            6 L2
       513587 ?GLUCO?
L8          0 L2 AND ?GLUCO?

=> s l2
L9          6 L2

=> d l9 1-6 ibib abs hitstr

L9   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        1998:597828  CAPLUS
DOCUMENT NUMBER:         130:1686
TITLE:                   The influence of side-chain modifications of
                         substrates on the activity of prolyl endopeptidase
AUTHOR(S):               Ludwig, H-H.; Vogel, D.; Rosche, F.; Hoffmann, T.;
                         Demuth, H-U.
CORPORATE SOURCE:        Department of Drug Biochemistry, Hans-Knoell-Institute
                         of Natural Product Research Jena, Halle, 06120,
                         Germany
SOURCE:                  Peptides 1996, Proceedings of the European Peptide
                         Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998),
                         Meeting Date 1996, 599-600.  Editor(s): Ramage,
                         Robert; Epton, Roger.  Mayflower Scientific:
                         Kingswinford, UK.
                         CODEN: 66RCA5
DOCUMENT TYPE:           Conference
LANGUAGE:                English
AB   Since proline serves as part of substrate recognition sites for protein
     kinases as well as for proline-specific peptidases, we argued that the
     activity of proline-specific peptidases might be modulated by
     post-translational modifications on amino acids in close proximity to
     proline within a substrate peptide chain.  We designed a series of related
     model peptides to study the influence of various side-chain modifications
     of these peptides on protein-peptide recognition and on the activity of
     proline-specific endopeptidases towards such structures.
IT   215675-56-2
     RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
     (Biological study); PROC (Process)
        (influence of side-chain modifications of substrates on activity of
        prolyl endopeptidase)
RN   215675-56-2  CAPLUS
CN   L-Lysine, L-lysyl-L-phenylalanyl-O-acetyl-L-threonyl-L-prolyl- (9CI)  (CA
     INDEX NAME)

Absolute stereochemistry.
```



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:287323 CAPLUS
DOCUMENT NUMBER: 126:340373
TITLE: Synthesis and kinetic properties of various side chain modified peptide derivatives as effectors of prolyl endopeptidase
AUTHOR(S): Ludwig, H.-H.; Vogel, D.; Demuth, H.-U.
CORPORATE SOURCE: Drug Biochem. Unit, Hans-Knoell-Institute Natural-Product Research Jena, Halle, D-06114, Germany
SOURCE: Perspectives on Protein Engineering '96, [International Conference], 5th, Montpellier, Fr., 1996 (1996), Paper No. 10, 5 pp.. Editor(s): Geisow, Michael J. BIODIGM: Bingham, UK.
CODEN: 64HIAR
DOCUMENT TYPE: Conference; (computer optical disk)
LANGUAGE: English

AB Proline serves as part of substrate recognition sites for protein kinases as well as for a highly selective group of proteolytic peptidases. This fact implies the assumption that the activity of proline-specific peptidases towards peptides might be modulated by post-translational modifications on amino acids in close proximity to proline within a peptide chain. According to the known substrate recognition motifs of such enzymes (MAP-kinases, HIV-protease, prolyl endopeptidase) we designed a series of structural related model peptides to study the influence of various side chain modifications of these peptides on protein-peptide recognition and on the activity of proline-specific endopeptidases towards such structures. The following series of Xaa-side chain substituted model compds. were prepd. and characterized by HPLC, MS and NMR (Xaa=Ser, Thr, Tyr): H-Lys-PHE-Xaa-Pro-Lys-OH H-Lys-Phe-Pro-Xaa-Lys-OH H-cyclo [-Lys-Phe-Xaa-Pro-Lys-] H-cyclo [-Lys-Phe-Pro-Xaa-Lys-]. Phosphorylation and the other hydroxy group modifications of the peptides were achieved during or after solid-phase synthesis. The evaluation of enzyme kinetic parameters was performed using HPLC and MALDI-TOF-mass spectrometry. Since proline-specific peptidases are co-localized with protein kinases and phosphatases, the obtained extreme variety of modification-dependent differences in the second-order rate consts. implies biol. significance of post-translational modifications of proline-contg. peptides.

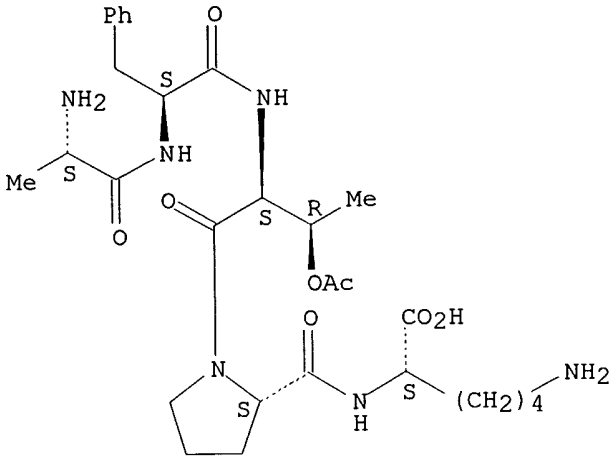
IT **189826-99-1**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(synthesis and kinetic properties of various side chain modified peptide derivs. as effectors of prolyl endopeptidase)

RN 189826-99-1 CAPLUS

CN L-Lysine, L-alanyl-L-phenylalanyl-O-acetyl-L-threonyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1990:572731 CAPLUS

DOCUMENT NUMBER: 113:172731

TITLE: A sensitive method for the determination of the primary amide function (RCONH2) in peptides by mass spectrometry

AUTHOR(S): Nutkins, Jennifer C.; Williams, Dudley H.

CORPORATE SOURCE: Chem. Lab., Univ. Cambridge, Cambridge, CB2 1EW, UK

SOURCE: Journal of the Chemical Society, Chemical Communications (1990), (11), 825-7
CODEN: JCCCAT; ISSN: 0022-4936

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several model peptides were trimethylsilylated and their fast ion bombardment mass spectra obtained; reaction was obsd. at hydroxy groups and primary amides only, amines and carboxy groups were obsd. in the underivitized form, and thus, in conjunction with std. procedures for the detn. of hydroxy groups, this methodol. represents a sensitive and extremely rapid means for the detection of primary amides in such mols.

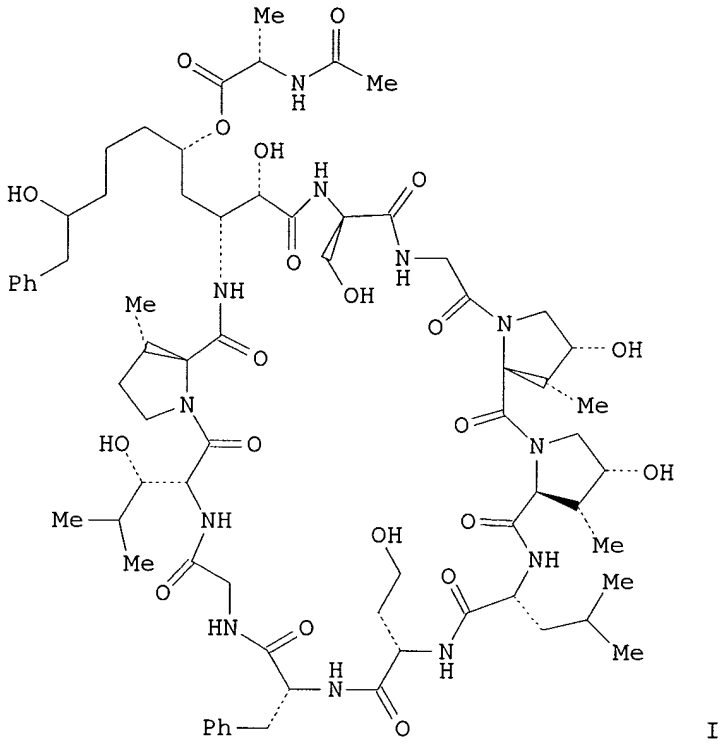
IT **129880-91-7 129880-92-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(amide group detection in, by mass spectrometry, trimethylsilylation in)

RN 129880-91-7 CAPLUS

CN L-Lysine, N6-acetyl-N2-[N2-[O-acetyl-N-[N-[N-[N2-[N-[1-[1-[O-acetyl-N-[N-(N-acetyl-L-.alpha.-glutamyl)-L-phenylalanyl]-L-threonyl]-L-prolyl]-L-prolyl]-L-valyl]-L-glutaminyl]-L-alanyl]-L-alanyl]-L-threonyl]-L-glutaminyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L9 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:128158 CAPLUS
DOCUMENT NUMBER: 108:128158
TITLE: Scytonemin A, a novel calcium antagonist from a blue-green alga
AUTHOR(S): Helms, Gregory L.; Moore, Richard E.; Niemczura, Walter P.; Patterson, Gregory M. L.; Tomer, Kenneth B.; Gross, Michael L.
CORPORATE SOURCE: Dep. Chem., Univ. Hawaii, Honolulu, HI, 96822, USA
SOURCE: Journal of Organic Chemistry (1988), 53(6), 1298-307
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A novel cyclic peptide, scytonemin A (I), possessing potent calcium antagonistic properties, is a major metabolite of the cultured cyanophyte Scytonema sp. (strain U-3-3). Vigorous acid hydrolysis of scytonemin A leads to L-alanine, 2 equivs. of glycine, L-homoserine (Hse), D-(2R,3S)-threo-3-hydroxyleucine (HyLeu), D-leucine, D-serine, L-(2S,3S)-trans-3-methylproline (MePro), 2 equiv. of L-(2S,3R,4R)-4-hydroxy-3-methylproline (HyMePro), D-phenylalanine, and (2S,3R,5S)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid (Ahda). Mild acid hydrolysis results in predominantly 2 acyclic peptides, viz. Ser-Gly-HyMePro-HyMePro-Leu-Hse and Phe-Gly-HyLeu-MePro-Ahda. Still milder hydrolysis results in selective cleavage of the homoseryl amide bond in scytonemin A to give an acyclic peptide, Phe-Gly-HyLeu-MePro-Ahda-Ser-Gly-HyMePro-HyMePro-Leu-Hse, with an N-acetylalanyl unit attached via an ester linkage to C-5 of Ahda and a homoseryl lactone unit at the C-terminus. State-of-the-art NMR and MS techniques were used to det. the

AUTHOR(S): Kameyama, Tsutomu; Sasaki, Kenichi
CORPORATE SOURCE: Tohoku Coll. Pharm., Sendai, Japan
SOURCE: Nippon Yakubutsugaku Zasshi (1970), 66(5), 503-10
CODEN: NIYZAM; ISSN: 0369-4461
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

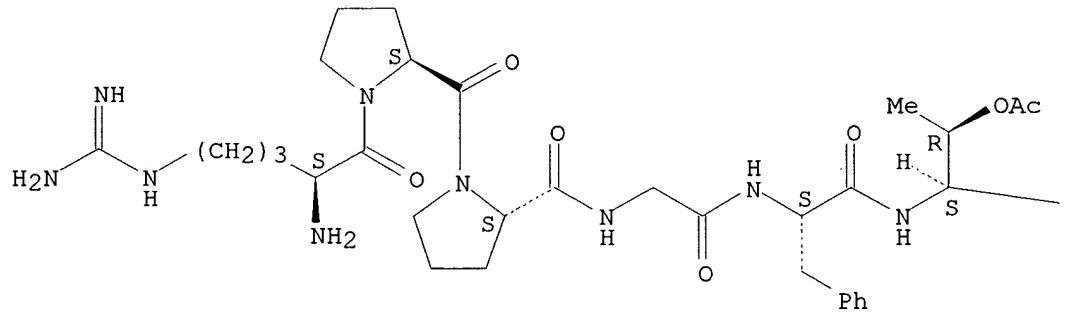
AB The hypotensive activity of 28 synthetic bradykinin (I) [58-82-2] analogs with varying amino acid residues in positions 3, 4, and 6 of I was compared with that of I in rats. None of the analogs tested was more potent than I, but the activities of 6-threonine-bradykinin [6120-63-4], 6-(O-acetylthreonine)-bradykinin [**5893-59-4**], 6-(O-acetylserine)-bradykinin [6109-89-3], and 3-alanine-3-glycine-bradykinin (sic) were relatively strong. Substitution of .beta.-alanine for an unspecified amino acid, which elongated the peptide chain of I by one methylene group, decreased activity. Leucine, isoleucine, or valine substitution in position 4 of I and 6-threonine-bradykinin also decreased activity. 3-Glycine-6-glycine-bradykinin [14997-52-5] and 3-lysine-bradykinin [16153-00-7] had low activity.

IT **5893-59-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypotensive activity of)

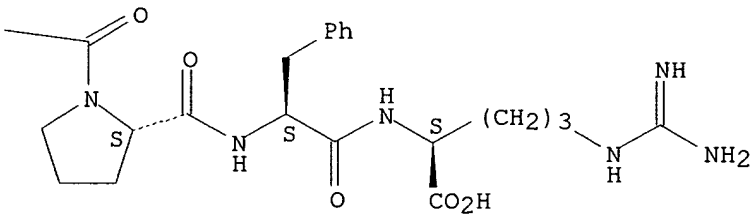
RN 5893-59-4 CAPLUS
CN Bradykinin, 6-(O-acetyl-L-threonine)- (9CI) (CA INDEX NAME)

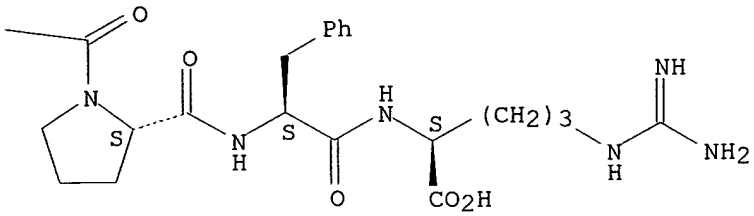
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B





L9 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1968:30040 CAPLUS
DOCUMENT NUMBER: 68:30040
TITLE: Synthesis of 4-L-valine-6-L-threonine-, 4-L-isoleucine- 6-L-threonine-, 4-L-leucine-6-L-threonine, 4-L-valine-, and 4-L-isoleucinebradykinin and their O-acetyl compounds
AUTHOR(S): Suzuki, Kenji; Abiko, Takashi
CORPORATE SOURCE: Tohoku Coll. Pharm., Sendai, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1967), 15(10), 1508-13
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis of the title analogs of bradykinin are described in which the glycine residue in the 4-position of bradykinin, 6-L-threonine-bradykinin, and their 6-O-acetyl derivs. are substituted for other amino acid residues having bulky side chains. The biol. activity of the ten analogs are compared with that of bradykinin on an isolated guinea pig ileum.

IT **16935-48-1P 16935-50-5P 16935-51-6P**
16935-52-7P 16944-37-9P 16964-30-0P
16964-31-1P 16964-32-2P 16964-33-3P
17021-43-1P 17037-12-6P 17037-13-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 16935-48-1 CAPLUS
CN Ornithine, N2-[N-[1-[N-[N-[N-(1-carboxy-L-prolyl)-L-isoleucyl]-3-phenyl-L-alanyl]-L-threonyl]-L-prolyl]-3-phenyl-L-alanyl]-N5-(nitroamidino)-, benzyl p-nitrobenzyl ester, acetate (ester), L- (8CI) (CA INDEX NAME)

Absolute stereochemistry.

```
> s glucosylceramide
          1070 GLUCOSYLCERAMIDE
           114 GLUCOSYLCERAMIDES
L1        1113 GLUCOSYLCERAMIDE
                (GLUCOSYLCERAMIDE OR GLUCOSYLCERAMIDES)

=> s l1 and glycosphingolipid?
          4253 GLYCOSPHINGOLIPID?
L2         425 L1 AND GLYCOSPHINGOLIPID?

=> s l2 and ?cancer?
        204545 ?CANCER?
L3          23 L2 AND ?CANCER?

=>
Uploading 10044869.str

L4      STRUCTURE UPLOADED

=> s l4 full
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




FULL SEARCH INITIATED 13:01:13 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     22 TO ITERATE

100.0% PROCESSED      22 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L5            0 SEA SSS FUL L4



L6           0 L5

=>
Uploading 10044869.str

L7      STRUCTURE UPLOADED

=> s l7 full
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




FULL SEARCH INITIATED 13:01:47 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     22 TO ITERATE

100.0% PROCESSED      22 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L8            0 SEA SSS FUL L7
```

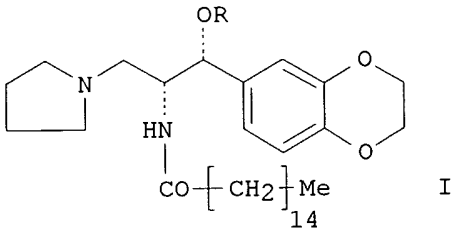
```
=> E SHAYMAN JAMES A/AU 25
E1            5      SHAYMAN J A/AU
E2            1      SHAYMAN JAMES/AU
E3           77 --> SHAYMAN JAMES A/AU
E4            1      SHAYMAN JAMES ALAN/AU
E5            1      SHAYMAN M A/AU
E6            1      SHAYMANOV A/AU
E7            1      SHAYMORDANOV I N/AU
E8            1      SHAYMURATOV V KH/AU
E9            1      SHAYNE ANDREW G/AU
E10           1      SHAYO ALBERTO/AU
E11           4      SHAYO C/AU
E12           4      SHAYO CARINA/AU
E13           1      SHAYO CARINA C/AU
E14           2      SHAYO MARCOS/AU
E15           3      SHAYO N B/AU
E16           2      SHAYO YUDA/AU
E17           1      SHAYO YUDA F/AU
E18           1      SHAYO YUDA FRANCIS/AU
E19           1      SHAYOTA MOFAK/AU
E20           1      SHAYOUB M/AU
E21           1      SHAYOUB MOHAMED/AU
E22           2      SHAYOVITS ANAT/AU
E23           3      SHAYOVITZ A/AU
E24           1      SHAYOVITZ ANAT/AU
E25           1      SHAYRIN S V/AU

=> S (E3) AND (GLUCOSYL?)
             77 "SHAYMAN JAMES A"/AU
          14029 GLUCOSYL?
L1           35 ("SHAYMAN JAMES A"/AU) AND (GLUCOSYL?)

=> S (E3) AND (CERAMID?)
             77 "SHAYMAN JAMES A"/AU
           8644 CERAMID?
L2           37 ("SHAYMAN JAMES A"/AU) AND (CERAMID?)

=> S (E3) AND (CANCER?)
             77 "SHAYMAN JAMES A"/AU
         189742 CANCER?
L3            2 ("SHAYMAN JAMES A"/AU) AND (CANCER?)

=> S (E3) AND (?TUMOR?)
             77 "SHAYMAN JAMES A"/AU
         387379 ?TUMOR?
L4            8 ("SHAYMAN JAMES A"/AU) AND (?TUMOR?)

=> s l2 and l4
L5            7 L2 AND L4

=> d l5 1-7 ibib abs

L5   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:978472  CAPLUS
DOCUMENT NUMBER:          138:39140
TITLE:                    Preparation of amino ceramide like prodrugs
                          for therapeutic use in the treatment of conditions
                          associated with altered glycosphingolipid levels
INVENTOR(S):              Shayman, James A.; Radin, Norman S.
PATENT ASSIGNEE(S):       USA
```

SOURCE: U.S. Pat. Appl. Publ., 13 pp., Cont.-in-part of U.S. Ser. No. 44,869.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002198240	A1	20021226	US 2002-134314	20020429
US 2002156107	A1	20021024	US 2002-44869	20020110

PRIORITY APPLN. INFO.: US 2001-260948P P 20010110
US 2001-262196P P 20010117
US 2002-44869 A2 20020110

OTHER SOURCE(S): MARPAT 138:39140
GI



I

AB Novel prodrugs of amino **ceramide**-like compds., such as R3CH2CH(NHCOR2)CH(R1)OR4 [R1 = arom., alicyclic, or aliph. groups; R2 = (CH2)nMe, n = 2-18; R3 = tertiary amine; R4 = CO(CH2)mMe, dihydropyridiylcarbonyl; m = 0; m .gtoreq. 1], were prepd for pharmaceutical use in the treatment of diseases, such as cancer, microbial or viral infections, and sphingolipidosis. The compds. of the present invention have improved glucosylceramide synthase (GlcCer) inhibition activity and are therefore highly useful in therapeutic methods for treating various conditions and diseases assocd. with altered glycosphingolipid levels. Thus, acetate I (R = COMe) was prepd. by acetylation of the corresponding alc I (R = H) with acetic anhydride by stirring in pyridine at rt for 2 days.

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:615591 CAPLUS
DOCUMENT NUMBER: 137:150282
TITLE: Amino **ceramide**-like compounds and therapeutic methods of use
INVENTOR(S): **Shayman, James A.**; Radin, Norman S.
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062777	A2	20020815	WO 2002-US808	20020110

WO 2002062777 A3 20021128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-260948P P 20010110
US 2001-262196P P 20010117

OTHER SOURCE(S): MARPAT 137:150282

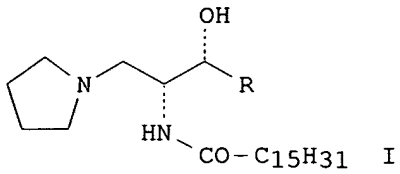
AB Novel prodrugs of amino **ceramide**-like compds. are provided which inhibit glucosyl **ceramide** (GlcCer) formation by inhibiting the enzyme GlcCer synthase, thereby lowering the level of glycosphingolipids. The compds. of the present invention have improved GlcCer synthase inhibition activity and are therefore highly useful in therapeutic methods for treating various conditions and diseases assocd. with altered glycosphingolipid levels.

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:50636 CAPLUS
DOCUMENT NUMBER: 134:115797
TITLE: Synthesis and GlcCer synthase inhibition of amino **ceramide**-like compounds
INVENTOR(S): **Shayman, James A.**; Radin, Norman S.
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001004108	A1	20010118	WO 2000-US18935	20000707
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1196406	A1	20020417	EP 2000-945332	20000707
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000012318	A	20020528	BR 2000-12318	20000707

PRIORITY APPLN. INFO.: US 1999-350678 A1 19990709
US 1999-350768 A 19990709
WO 2000-US18935 W 20000707

OTHER SOURCE(S): MARPAT 134:115797
GI



I

AB Synthesis of amino **ceramide**-like compds. (I) (R = 3,4-ethylenedioxyphenyl, 4-hydroxyphenyl) are disclosed which inhibit glucosyl **ceramide** (GlcCer) formation by inhibiting the enzyme GlcCer synthase, thereby lowering the level of glycosphingolipids. Thus, I (R = 4-HOC6H4) (II) is prepd. from 4-hydroxyacetophenone by hydroxy protection with benzyl bromide followed by bromination of acetyl, amination of bromide, amidation with palmitoyl chloride, condensation with formaldehyde and pyrrolidine, ketone redn., debenzylation and resoln. with chiral chromatog. II shows an IC50 of 0.5 in GlcCer synthase inhibition assay. The compds. of the present invention have improved GlcCer synthase inhibition activity and are therefore highly useful in therapeutic methods for treating various conditions and diseases assocd. with altered glycosphingolipid levels.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:321421 CAPLUS
DOCUMENT NUMBER: 126:288113
TITLE: Aminoceramide-like compounds and therapeutic methods of use
INVENTOR(S): **Shayman, James A.**; Radin, Norman S.
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9710817	A1	19970327	WO 1996-US14219	19960905

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1995-4047P P 19950920
OTHER SOURCE(S): MARPAT 126:288113

AB Aminoceramide-like compds. are provided which inhibit glucosylceramide (GlcCer) formation by inhibiting the enzyme GlcCer synthase, thereby lowering the level of glycosphingolipids. The compds. of the invention have improved GlcCer synthase inhibition activity and are therefore highly useful in therapeutic methods for treating various conditions and diseases assocd. with altered glycosphingolipid levels.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:13942 CAPLUS
DOCUMENT NUMBER: 124:113608
TITLE: **Ceramide** formation during heat shock: a potential mediator of .alpha.B-crystallin transcription
AUTHOR(S): Chang, Yan; Abe, Akira; **Shayman, James A.**
CORPORATE SOURCE: Dep. Int. Med., Univ. Michigan, Ann Arbor, MI, 48109-0676, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(26), 12275-9
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Ceramide** has been identified as a potential second messenger that may mediate cell differentiation and apoptosis after exposure to hormonal agonists such as 1.alpha.,25-dihydroxyvitamin D3, **tumor** necrosis factor .alpha., or .gamma.-interferon. The secondary cellular events that follow **ceramide** generation remain undefined. The authors report that in NIH WT-3T3 cells, **ceramide** induces an enhancement of gene transcription of .alpha.B-crystallin, a small heat shock protein. The levels of .alpha.B-crystallin, as measured by Northern blot and immunoblot analyses, were increased by the addn. of an exogenous short-chain **ceramide**, N-acetylsphingosine, or by increasing endogenous intracellular **ceramide** by inhibition of glucosylceramide synthase. Similar effects were not seen in the expression of the closely related gene, Hsp25. To ascertain whether **ceramide**-mediated gene transcription was a feature of the heat shock response, cell **ceramide** was measured in heat shocked cells and obsd. to be elevated 2-fold immediately upon the return of cells to 37.degree.. Thus **ceramide** formed after heat shock treatment of 3T3 cells may mediate the transcription events assocd. with the cell stress response.

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:471614 CAPLUS
DOCUMENT NUMBER: 122:281432
TITLE: Structural and stereochemical studies of potent inhibitors of glucosylceramide synthase and **tumor** cell growth
AUTHOR(S): Abe, Akira; Radin, Norman S.; **Shayman, James A.**; Wotring, Linda L.; Zipkin, Robert E.; Sivakumar, Ramachandran; Ruggieri, Jeffrey M.; Carson, Kenneth G.; Ganem, Bruce
CORPORATE SOURCE: Dep. Internal Medicine, Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Journal of Lipid Research (1995), 36(3), 611-21
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs and homologs of PDMP were synthesized, based on its structure (D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol). This compd. had previously been found to block the synthesis of GlcCer (glucosylceramide). Increasing the acyl chain length from 10 to 16 carbon atoms greatly enhanced the efficacy of the enzyme inhibitor, as did the use of a less polar cyclic amine, esp. a pyrrolidine instead of a morpholine ring. Replacement of the Ph ring by a chain corresponding to sphingosine also yielded a strongly inhibitory material. By using a chiral synthetic route, we showed that the isomers active against GlcCer synthase had the R,R-(D-threo)-configuration. However, strong inhibition of the growth of human cancer cells in plastico was produced by both the threo and erythro racemic compds., showing involvement of an addnl. factor (beyond simple depletion of cell glycosphingolipids by blockage of GlcCer synthesis). The growth arresting effects could be correlated with increases in cellular **ceramide** and diglyceride levels. The aliph. pyrrolidino compd. was strongly inhibitory toward the glucosyltransferase and produced almost complete depletion of glycolipids, but did not inhibit growth or cause an accumulation of **ceramide**. Attempts were made to see whether the differences in growth effects could

be attributed to the influence of the inhibitors on related enzymes (**ceramide** and sphingomyelin synthase and **ceramidase** and sphingomyelinase). While some stimulation of enzyme activity was noted, particularly at high inhibitor concns. (50 .mu.M), these findings did not explain the differing effects of the different inhibitors. The best inhibitors of GlcCer synthase compared favorably in efficacy with some cancer chemotherapeutic drugs in current use when tested with a battery of human cancer cells.

L5 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:242217 CAPLUS
DOCUMENT NUMBER: 120:242217
TITLE: Dissociation of endogenous cellular **ceramide** from NF-.kappa.B activation
AUTHOR(S): Betts, Jonathan C.; Agranoff, Adam B.; Nabel, Gary J.; **Shayman, James A.**
CORPORATE SOURCE: Dep. Intern. Med., Univ. Michigan, Ann Arbor, MI, 48109-0676, USA
SOURCE: Journal of Biological Chemistry (1994), 269(11), 8455-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The participation of cell **ceramide** in **tumor** necrosis factor (TNF)-.alpha.-stimulated NF-.kappa.B activation in Jurkat T cells and HL-60 cells was studied. TNF-.alpha. readily stimulated NF-.kappa.B activity in both cell lines as assayed by electrophoretic mobility shift assay and the use of a human immunodeficiency virus-chloramphenicol acetyltransferase reporter construct. However, TNF-.alpha. stimulation did not increase cell **ceramide** levels in either cell line. The exogenous addn. of a short chain **ceramide**, N-acetylsphingosine, to Jurkat cells had no effect on NF-.kappa.B activity. When Jurkat T cells were exposed to the glucosylceramide synthase inhibitor, 1-phenyl-2-decanoylamino-3-morpholino-1-propanol, endogenous **ceramide** levels increased 4-fold. The increase in **ceramide**, however, did not result in NF-.kappa.B activation nor did it potentiate TNF-.alpha. or phorbol ester-stimulated activity. The authors conclude that TNF-.alpha.-induced NF-.kappa.B activation occurs in Jurkat and HL-60 cell lines that do not demonstrate an increase in TNF-.alpha.-induced **ceramide**. Increasing **ceramide** levels by the addn. of short chain **ceramides** or the use of a glycosylceramide synthase inhibitor can be dissocd. from activation of NF-.kappa.B by TNF-.alpha..